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Transient [3,3] Cope rearrangement of 3,3-dicyano-1,5-dienes: computational analysis and 2-step synthesis of arylcycloheptanes†

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A simple and modular route to arylcycloheptene scaffolds is reported. The two-step route from Knoevenagel adducts and allylic electrophiles is made possible through the design of a Cope rearrangement that utilizes a "traceless" activating group to promote an otherwise thermodynamically unfavorable transformation. Experimentally, the [3,3] rearrangement occurrs transiently at room temperature with a computed barrier of 19.5 kcal mol^{-1}, which ultimately allows for three-component bis-allylation. Ring-closing metathesis delivers the arylcycloheptane and removes the activating group. This report describes the design and optimization of the methodology, scope and mechanistic studies, and computational analysis.

Introduction

Structurally complex natural products are promising leads for treating diseases[1] and are commonly acquired by isolation and semisynthesis.[2] *De novo* synthesis of complex bioactive molecules and their analogs is a modern synthetic challenge.[3,4] The most successful examples address synthetic ideality:[5] efficiency, practicality, and scalability. From a drug discovery perspective, modularity needs to also be addressed.

We and others are interested in designing practical routes to polycyclic architectures that are simple and efficient from abundant starting material classes.[6] Adhering to these requirements will result in routes amenable to target and target-analog synthesis. Inspired by bioactive aryl-cycloheptanes (Fig. 1) which include terpenes (the frondosins,[7] liphagal,[8] pharbinilic acid[9]), resveratrol-derivatives (vitisinol C,[10] ampelopsin A[11]), alkaloids[12] (ambiguine,[13] actinophyllic acid,[14] exotine B[15]), and marketed drugs (irosustat[16]) and drug leads (the synthetic SIRT1 inhibitor[17]) (Scheme 1), we hypothesized that 1,5-dienes **A** and an allylic electrophile **B**, could be converted to the aryl-cycloheptane scaffold **C** over, in theory, a simple procedure involving a Cope rearrangement, deconjugative allylation, and ring-closing metathesis (RCM) (Scheme 1).[6b,c] Notably, 1,5-dienes of type **A** are prepared by a simple and convergent two-step protocol from ketones, malononitrile, and cinnamyl electrophiles: all abundant starting material classes.[6b] Unfortunately, in model studies, the Cope rearrangement is not thermodynamically favorable due to styrene-deconjugation.[6b]

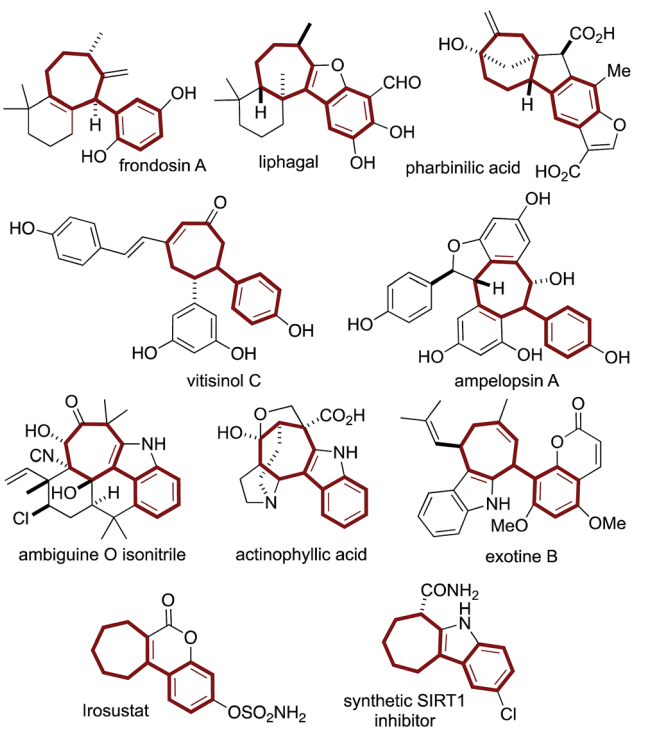

Fig. 1 The arylcycloheptane scaffold is common to terpenoid-, resveratrol-, alkaloidal-, and synthetic drug molecules.

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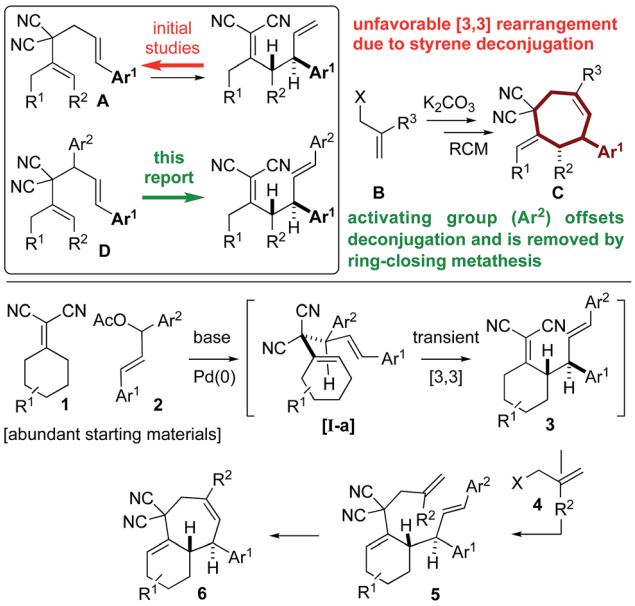
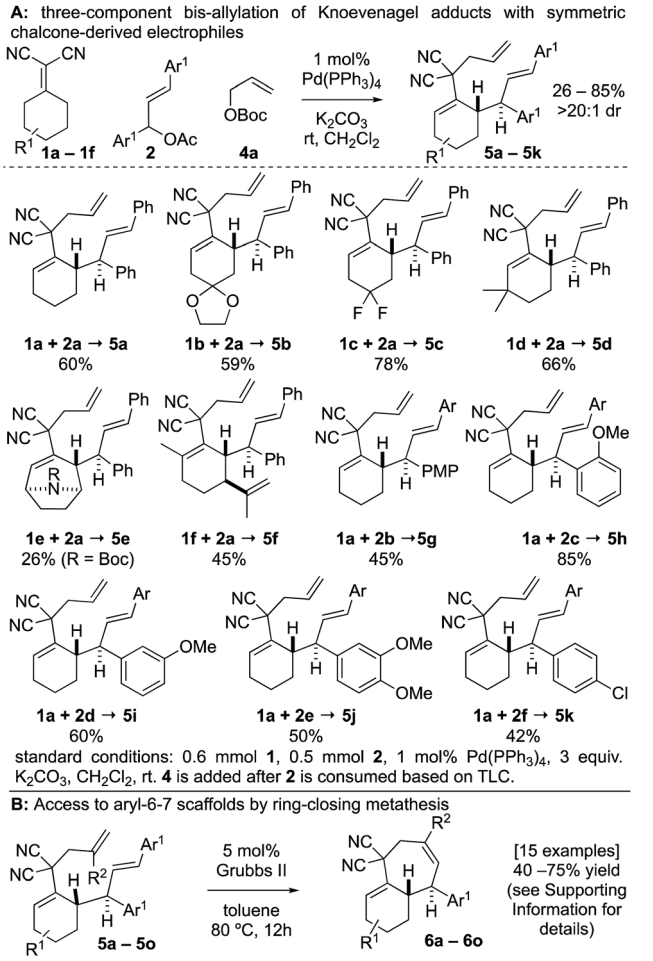


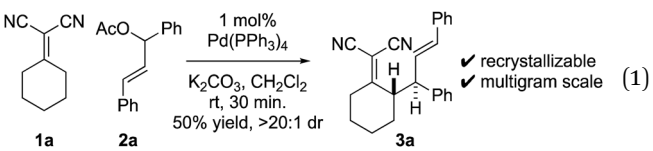
Scheme 1 Overcoming thermodynamic limitations of [3,3] Cope rearrangements though the introduction of a "traceless" activating group, which is removed during the RCM step.

To combat the poor conversions observed with 1,5-dienes **A**, we hypothesized that the 4,6-diaryl-1,5-dienes **D** would be more reactive toward thermal rearrangement as styrene deconjugation is offset (Scheme 2).[6b,18] Furthermore, the exact same products **C** can be accessed as the [3,3]-promoting aryl group (Ar2) is removed in the ring-closing metathesis step. To reiterate, the additional aryl group serves to provide a driving-force for an otherwise unfavorable [3,3] rearrangement and is "traceless" upon RCM. Herein we report that Knoevenagel adducts **1** and chalcone-derived electrophiles **2** undergo deconjugative alkylation to [**I-a**] followed by a transient [3,3] rearrangement (unexpectedly occurring at room-temperature with a calculated barrier of 19.5 kcal mol^{-1}) to yield the γ-allylated Knoevenagel adduct **3**. Deconjugative alkylation with allylic electrophiles **4** yields the bis-allylated building blocks **5** in one-step from **1**, **2**, and **4**, which undergo facile RCM to arylcycloheptenes **6**.



Scheme 2 Scope of two-step arylcycloheptene synthesis.

scaffolds **5a–5k** (Scheme 2A) which are routinely converted to arylcycloheptenes by ring-closing metathesis (Scheme 2B).



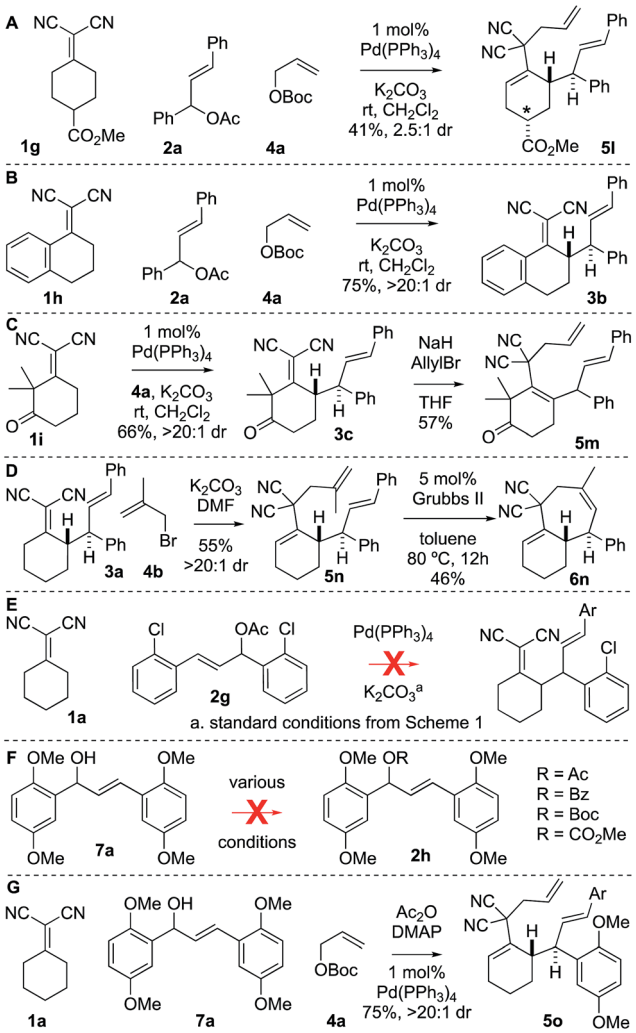
(1)

Results and discussion

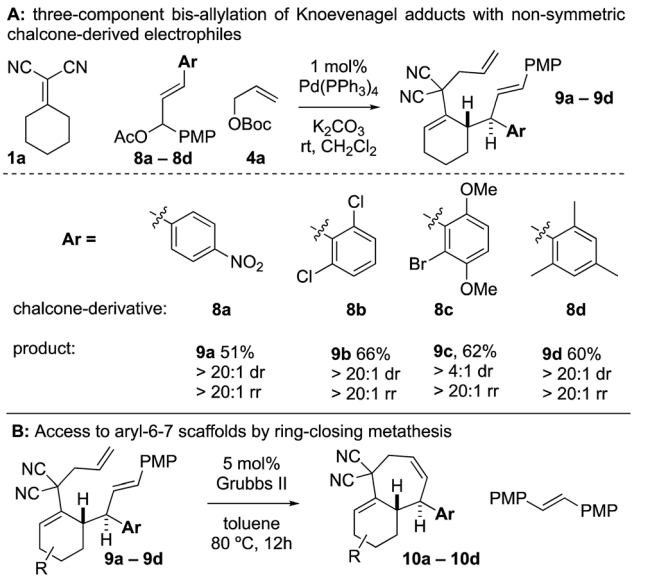
At the outset of our studies, we examined model Knoevenagel adduct **1a** and chalcone-derived electrophile **2a** and uncovered that by Pd(0)-catalysis, the molecules couple yielding the γ-allylated scaffold **3a** (eqn (1)). The reaction was efficient, diastereoselective, scalable, and the product can be recrystallized. The regioselectivity was also unexpected as alkyl electrophiles (*e.g.* alkyl halides and allyl acetates/carbonates) tend to yield deconjugative alkylation products.[19,20] Thus, this result raises the question as to whether **3** is accessed by a [3,3] rearrangement[21] as originally proposed or by a direct γ-allylation mechanism.[20] This connectivity is nonetheless welcomed as the high acidity of the Knoevenagel adduct remains unchanged allowing for three-component coupling directly to bis-allylated

The three-component coupling tolerated a wide array of cyclic Knoevenagel adducts **1a–1f** and symmetric chalcone-derived electrophiles **2a–2f** (Scheme 2A). The mild reaction is tolerant to ketal (**5b**), *gem*-difluoro (**5c**), carbamate (**5e**), and alkene functional groups (**5f**). **5d** was prepared by a regioselective deprotonation to initiate the transformation. A variety of substitution patterns on the arene could also be incorporated including *p*-, *o*-, *m*-methoxy (**5g–5i**), dimethoxy (**5j**), and *p*-chloro (**5k**) substitutions.

There were several other notable experiments performed related to the scope of the Knoevenagel adduct bis-allylation protocol (Scheme 3). Pro-chiral Knoevenagel adducts with a remote stereocenter (*e.g.* **1g**) gave rise to diastereomeric mixtures (Scheme 3A). Also, when examining the tetralone-



Scheme 3 Other studies related to the Knoevenagel adduct bis-allylation protocol.



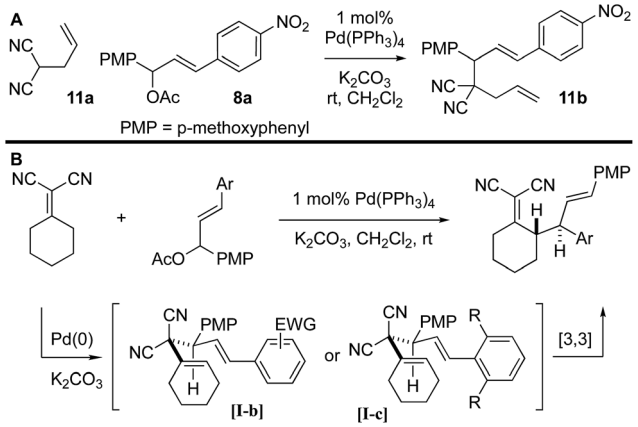
Scheme 4 Exploration of nonsymmetric chalcone-derivatives in arylcycloheptane synthesis.

derived Knoevenagel adduct **1h** for three-component bis-alkylation reactivity, only two-component coupling was observed to **3b** (Scheme 3B). Similarly, this was observed with Knoevenagel adduct **1i**. However, deprotonation of sterically encumbered γ-C–H's can be achieved with NaH as the base (**5m**, Scheme 3C). The sequence can also be performed with 2-substituted allylic electrophiles ultimately yielding trisubstituted olefins by RCM (Scheme 3D). Next, the electron-deficient chalcone-derivative **2g** did not react under the standard conditions (0% conversion), likely due to challenges associated with the oxidative addition step (Scheme 3E). Attempts to make the activated chalcone-derived electrophile **2h** were unsuccessful (Scheme 3F). We suspected that the issue might be that acylation is occurring, but the acetate/carbonate is prone to hydrolysis back to the alcohol under standard work-up conditions (extraction conditions, silica gel, *etc.*). In agreement with this, successful coupling was achieved directly from the alcohol **7a** using an *in situ* acylation strategy (Scheme 3G).

When examining non-symmetric chalcone-derived electrophiles **8a–8d** with Knoevenagel adduct **1a**, it was uncovered that diastereo- and regioselective transformation to the bis-allylated products **9a–9d** could be achieved (Scheme 4). The electrophiles bore a *p*-methoxyphenyl (PMP) and a variable arene (*p*-nitrophenyl (**8a**), 2,6-dichloro (**8b**), 2-bromo-3,6-dimethoxyphenyl (**8c**), and 2,4,6-trimethylphenyl (**8d**)). In all cases, the variable arene was installed at the allylic position. Thus, upon ring-closing metathesis, the PMP-group was removed and the variable-aryl-cycloheptenes **10a–10d** were prepared.

It was not clear whether the mechanism of the initial coupling between the Knoevenagel adduct and the chalcone-derived allylic electrophile occurs by the originally conceived deconjugative alkylation/transient [3,3] rearrangement sequence or by a direct γ-allylation mechanism. The regioselectivity observed in Scheme 4 suggests that the reaction is proceeding by low-barrier Cope rearrangement (occurring at room-temperature). This is surprising as related 3,3-dicyano-1,5-dienes do not undergo rearrangement until heated >120 °C.[6b] Furthermore, Cope rearrangements occurring at room temperature usually bear a strain element[22] or are "oxy-Cope" substrates.[23] Consider the following data: (a) allyl malononitrile **11a** reacts with **7a** to yield product **11b** where the PMP group, not the *p*-nitrophenyl group, is at the allylic position (Scheme 6A). This result is opposite to the connectivity in **9a** (Scheme 5). (b) The regioselectivity of allylation with **8b–8d** is such that the sterically bulky arene is at the allylic position on the bis-allylated building blocks **9b–9d**. As shown in Scheme 5B, we suggest that deconjugative alkylation occurs first yielding the 1,5-dienes [**I-a**/**b**]. This transformation is either electronically **[I-b]** or sterically **[I-c]** driven (or both). Cope rearrangement then yields the γ-allylated product with connectivity that matches the products from bis-allylation (Scheme 4).

To probe whether a room-temperature Cope rearrangement of 4,6-diaryl-3,3-dicyano-1,5-dienes was reasonable,[24] we performed computational studies for the synthesis of **3a** (Fig. 2).



Scheme 5 γ-Allylation occurs by a transient Cope rearrangement.

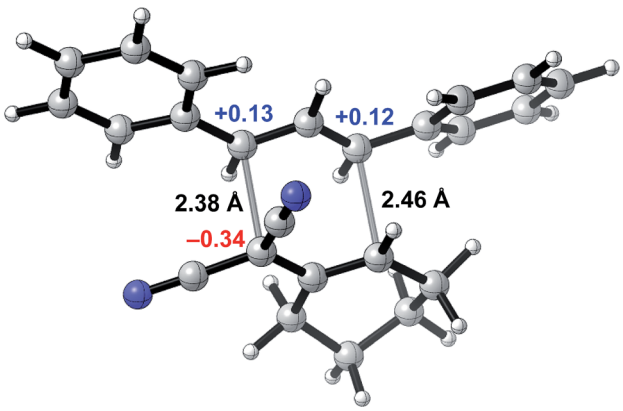
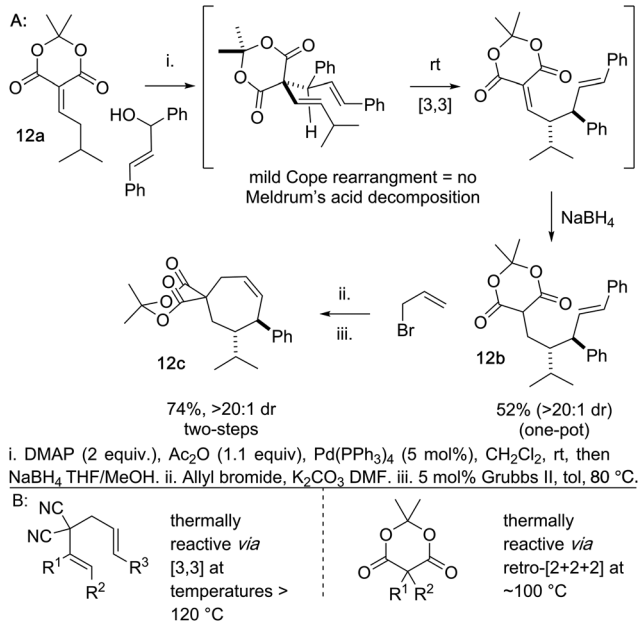


Fig. 2 Transition state for the Cope rearrangement leading to the formation of **3a** computed *via* density functional theory.

Density functional theory calculations showed that the Cope rearrangement was exergonic by 8.6 kcal mol^{-1} and had an unusually low free energy barrier of 19.5 kcal mol^{-1}, corresponding to a half-life of 23 seconds at room temperature. To explain the facility of this Cope rearrangement at room temperature, we investigated bond lengths and atomic charges in the transition state (Fig. 1). The transition state revealed substantial dissociative character (2.38 Å and 2.46 Å for the breaking and forming bonds respectively) and significant charge separation, with a stabilized negative charge (−0.34*e*) alpha to the two nitrile groups and stabilized positive charges (+0.13*e* and +0.12*e*) at the two benzylic positions. The ability of the nitrile groups and phenyl groups to stabilize each transition state fragment *via* conjugation accounts for the low barrier of this Cope rearrangement. All structures were optimized at the M06-2X/6-31+G(d) level of theory with single-point energy corrections computed at the M06-2X-D3/6-311++G(2d,2p) level of theory with dichloromethane CPCM solvent; partial charges were computed *via* NBO analysis and hydrogen atom charges were summed into the neighboring heavy atom.

Another beneficial consequence of the Cope rearrangement being exceedingly mild is we can begin to prepare cycloheptene scaffolds bearing an embedded Meldrum's acid moiety *in lieu* of



Scheme 6 (A) Meldrum's acid-derived Knoevenagel adducts can undergo deconjugative alkylation/Cope rearrangement. (B) This would not possible with higher energy Cope rearrangements because Meldrum's acid is unstable.

the *gem*-dinitrile (Scheme 6). Meldrum's acid moieties are excellent handles for functional group interconversion.[25] This was previously not possible because the standard Cope rearrangements of this type occur at temperatures >120 °C and Meldrum's acid derivatives tend to decompose to ketene, CO_2, and acetone at temperatures lower than this.[26] As a preliminary example of this, we coupled the Meldrum's acid–isovaleraldehyde Knoevenagel adduct **12a** and the chalcone-derived alcohol directly to **12b** by a one-pot alcohol activation, Pd-catalyzed deconjugative allylation-transient-Cope sequence, and alkylidene reduction. In two additional simple steps the Meldrum's acid embedded arylcycloheptene **12c** is accessed.

Conclusions

Inspired by arylcycloheptane architectures, we have uncovered a two-step route to such core scaffolds that is amenable to structural change due to the concise synthetic sequence from abundant starting material classes. The route is made possible through the development of a [3,3] promoting group strategy for driving forward otherwise thermodynamically unfavorable Cope rearrangements. The surprisingly low-barrier Cope rearrangement, occurring transiently with a calculated barrier of 19.5 kcal mol^{-1}, ultimately enabled a one-pot bis-allylation protocol to be developed for Knoevenagel adducts. Future studies include improving the scope, applying the method in target/target-analog synthesis, and rendering the strategy enantioselective. The [3,3] "promoting group strategy" described herein may be a general manifold for promoting many other unfavorable [3,3] rearrangements. We plan to examine this broadly too.

Conflicts of interest

There are no conflicts to declare.

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